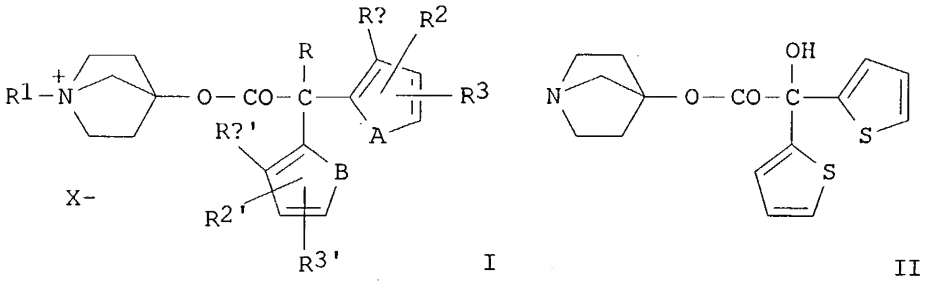
STN STRUCTURE SEARCH 7-12-04

=> d ibib abs hitstr 1-27

L4 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:855068 CAPLUS
DOCUMENT NUMBER: 139:350647
TITLE: Preparation of 1-azabicyclo[2.2.1]heptan-4-ol esters as muscarinic receptor M3 ligands for the treatment of
INVENTOR(S): Grauert, Matthias; Hoffmann, Matthias; Pieper, Michael P.; Speck, Georg; Breitfelder, Steffen
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Gmbh & Co. Kg, Germany
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

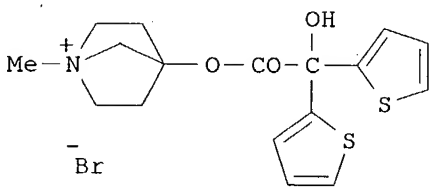
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10216333	A1	20031030	DE 2002-10216333	20020413
DE 10316660	A1	20040226	DE 2003-10316660	20030411

PRIORITY APPLN. INFO.: DE 2002-10216333 A1 20020413
OTHER SOURCE(S): MARPAT 139:350647
GI



I

II



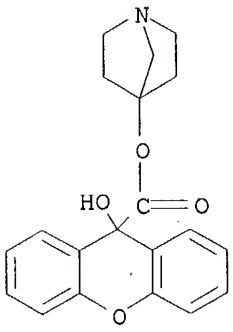
III

AB Title compds. I [X- = anion, e.g., halo, sulfate, phosphate, etc.; A, B = O, S, NH, etc.; R1 = H, (un)substituted alkyl; R2, R3, R2', R3, R3' = H, alkyl, alkoxy, etc.; Rx, Rx' = H, alkyl, alkoxy, etc.] and their pharmaceutically acceptable salts and formulations were prepared Foe example, N-alkylatonod amine II, e.g., prepared from 1-azabicyclo[2.2.1]heptan-4-ol and α-hydroxy-α-2-thienyl-2-thiopheneacetic Me ester, afforded ester III in 78% yield. In muscarinic receptor M3 ligand binding assays, 4-examples of compds. I exhibited Ki values < 100 nM.

IT **618114-93-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

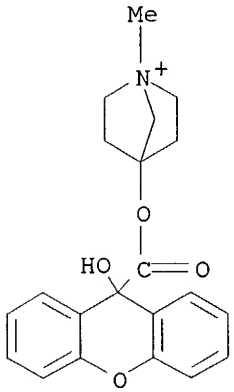
(Reactant or reagent)
(intermediate; preparation of 1-azabicyclo[2.2.1]heptan-4-ol esters as muscarinic receptor M3 ligands for the treatment of)

RN 618114-93-5 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 9-hydroxy-, 1-azabicyclo[2.2.1]hept-4-yl ester (9CI) (CA INDEX NAME)



IT **618114-89-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of 1-azabicyclo[2.2.1]heptan-4-ol esters as muscarinic receptor M3 ligands for the treatment of)

RN 618114-89-9 CAPLUS
CN 1-Azoniabicyclo[2.2.1]heptane, 4-[[(9-hydroxy-9H-xanthen-9-yl)carbonyl]oxy]-1-methyl-, bromide (9CI) (CA INDEX NAME)



● Br^-

L4 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:50645 CAPLUS
DOCUMENT NUMBER: 134:116110
TITLE: Synthesis of novel quinuclidine derivatives for the manufacture of medicament for use as antimuscarinic agents
INVENTOR(S): Fernandez Forner, Dolors; Prat Quinones, Maria; Buil

Albero, Maria Antonia
PATENT ASSIGNEE(S): Almirall Prodesfarma S.A., Spain
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

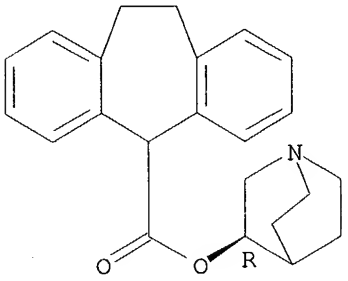
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004118	A2	20010118	WO 2000-EP6469	20000707
WO 2001004118	A3	20010719		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ES 2165768	A1	20020316	ES 1999-1580	19990714
ES 2165768	B1	20030401		
BR 2000012434	A	20020402	BR 2000-12434	20000707
EP 1200431	A2	20020502	EP 2000-951361	20000707
EP 1200431	B1	20030326		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200200768	T2	20020722	TR 2002-20020076820000707	
JP 2003504368	T2	20030204	JP 2001-509727	20000707
AT 235492	E	20030415	AT 2000-951361	20000707
EE 200200017	A	20030415	EE 2002-17	20000707
PT 1200431	T	20030731	PT 2000-951361	20000707
ES 2193098	T3	20031101	ES 2000-951361	20000707
ZA 2002000232	A	20030410	ZA 2002-232	20020110
NO 2002000180	A	20020313	NO 2002-180	20020114
BG 106301	A	20020830	BG 2002-106301	20020114
US 2003055080	A1	20030320	US 2002-47464	20020114
US 6750226	B2	20040615		
HK 1042487	A1	20030718	HK 2002-103992	20020529
US 2004132768	A1	20040708	US 2003-740264	20031217

PRIORITY APPLN. INFO.: ES 1999-1580 A 19990714
WO 2000-EP6469 W 20000707
US 2002-47464 A3 20020114

OTHER SOURCE(S): MARPAT 134:116110
GI

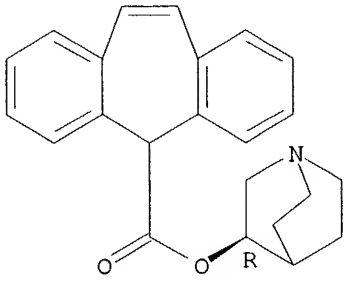
RN 320348-08-1 CAPLUS
CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



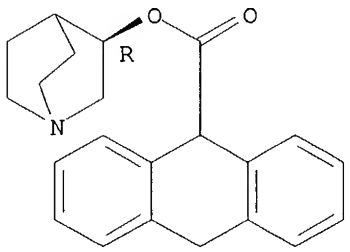
RN 320348-09-2 CAPLUS
CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



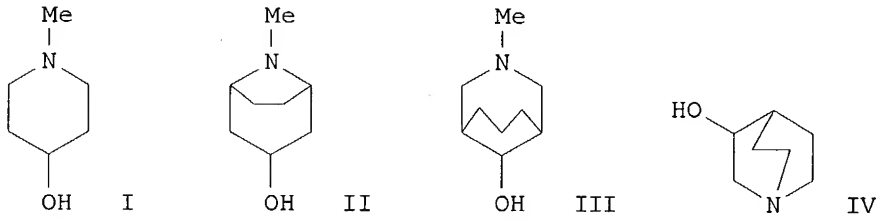
RN 320348-10-5 CAPLUS
CN 9-Anthracenecarboxylic acid, 9,10-dihydro-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:159472 CAPLUS
DOCUMENT NUMBER: 130:251985
TITLE: Stereochemistry of the heterocyclic alcohols containing piperidine unit
AUTHOR(S): Gao, Shou-Hai; Hu, Wen-Xiang; Yun, Liu-Hong
CORPORATE SOURCE: Institute of Pharmacology and Toxicology, Academy of

Military Medical Sciences, Beijing, 100850, Peop. Rep. China
SOURCE: Gaodeng Xuexiao Huaxue Xuebao (1999), 20(2), 232-236
CODEN: KTHPDM; ISSN: 0251-0790
PUBLISHER: Gaodeng Jiaoyu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI

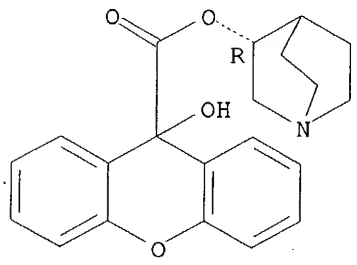


AB The stereochem. of the heterocyclic alcs. (1-4 = I-IV) containing piperidine unit was studied on the basis of the results of mol. mechanics and quantum chemical calcns. The results showed that there existed non-classical orbital super-conjugated interactions between the nitrogen atom and oxygen atom which caused the conformations to be more stable when the hydroxylic group lay at axial than at equatorial with respect to the piperidine ring in compound 1 and compound 3. If the axial hydrogen atoms at C2 and C6 positions in the piperidine ring were substituted, or the mol. existed in the polar solns., this non-classical orbital super-conjugated interactions would be much weaker. In this case, the conformations were more stable when the hydroxylic group was equatorial.

IT **221671-35-8 221671-36-9 221671-37-0**
221671-38-1 221671-39-2 221671-40-5
221671-43-8 221671-44-9 221671-45-0
221671-46-1 221671-47-2 221671-48-3
RL: PRP (Properties)
(mol. mechanics and AM1 study of the conformation of heterocyclic piperidine alcs. and of piperidinyl hydroxycarboxylates)

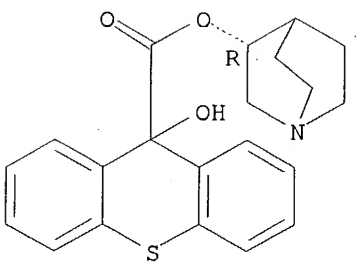
RN 221671-35-8 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 9-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



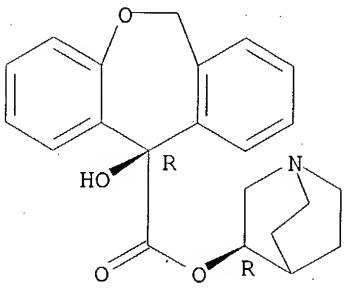
RN 221671-36-9 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 9-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



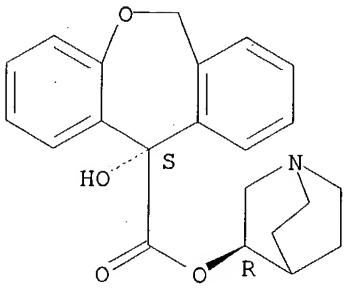
RN 221671-37-0 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, (11R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



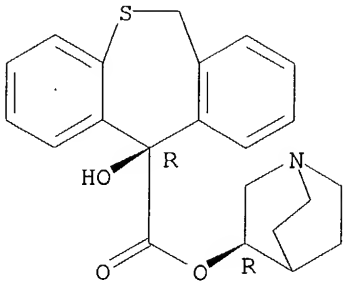
RN 221671-38-1 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, (11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



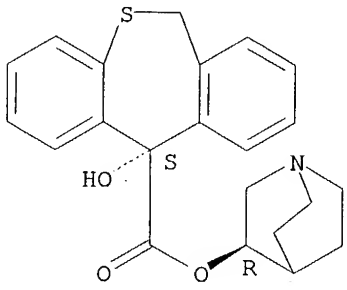
RN 221671-39-2 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, (11R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



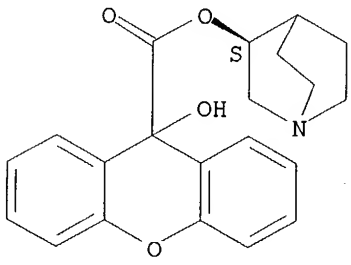
RN 221671-40-5 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, (11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



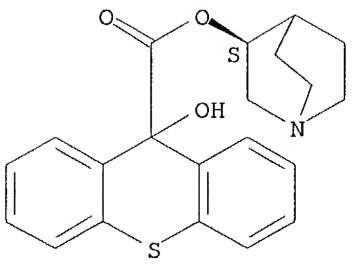
RN 221671-43-8 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 9-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



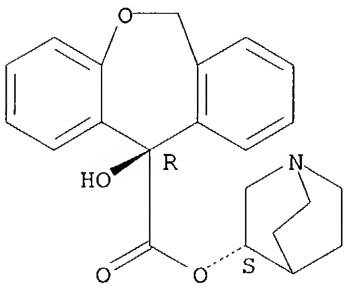
RN 221671-44-9 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 9-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



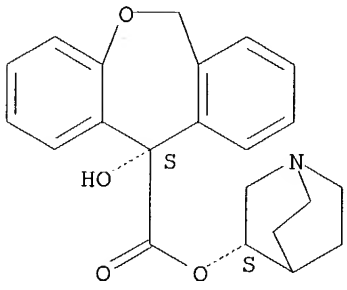
RN 221671-45-0 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester, (11R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



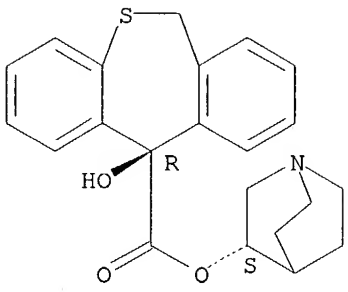
RN 221671-46-1 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester, (11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



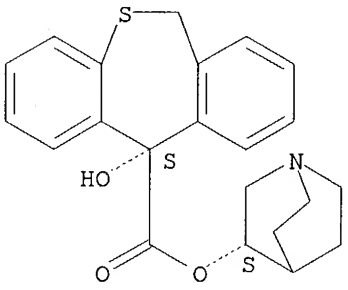
RN 221671-47-2 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester, (11R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 221671-48-3 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, (3S)-1-azabicyclo[2.2.2]oct-3-yl ester, (11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:632704 CAPLUS
DOCUMENT NUMBER: 127:272807
TITLE: Administration of pirenzepine, methylscopolamine and other muscarinic receptor antagonists, alone or in combination with prolactin-inhibiting compds, for treatment of lipid metabolism disorders
INVENTOR(S): Cincotta, Anthony H.; Meier, Albert H.; Wilson, John M.
PATENT ASSIGNEE(S): General Hospital Corporation, USA; Board of Supervisors of Louisiana State University and Agricultural and Mechanical College
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 5,585,347.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5668155	A	19970916	US 1994-263607	19940620
JP 10072372	A2	19980317	JP 1997-177080	19910110
US 5344832	A	19940906	US 1991-719745	19910624
US 5585347	A	19961217	US 1992-995292	19921222
US 5468755	A	19951121	US 1993-158153	19931124
US 5496803	A	19960305	US 1994-287066	19940808
US 5716932	A	19980210	US 1995-450917	19950526
US 5716933	A	19980210	US 1995-452388	19950526

US 5731287	A	19980324	US 1995-452389	19950526
US 5700795	A	19971223	US 1995-458085	19950601
US 5712265	A	19980127	US 1995-458061	19950601
US 5756513	A	19980526	US 1995-459020	19950602
US 5716962	A	19980210	US 1995-465820	19950606
US 5866584	A	19990202	US 1995-465818	19950606
CA 2193530	AA	19951228	CA 1995-2193530	19950620
WO 9535110	A1	19951228	WO 1995-US9056	19950620
W: AU, BR, CA, CZ, FI, HU, JP, MX, NO, NZ, SK				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9531345	A1	19960115	AU 1995-31345	19950620
AU 702772	B2	19990304		
EP 764026	A1	19970326	EP 1995-927259	19950620
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10507159	T2	19980714	JP 1995-502626	19950620
ZA 9505415	A	19960409	ZA 1995-5415	19950629
US 6004972	A	19991221	US 1998-103105	19980623

PRIORITY APPLN. INFO.:

US 1988-192332	B2	19880510
US 1990-463327	B2	19900110
US 1991-719745	A2	19910624
US 1992-995292	A2	19921222
JP 1991-65737	A3	19910110
US 1991-813135	B1	19911223
US 1992-999685	B1	19921231
US 1993-158153	A1	19931124
US 1994-263607	A1	19940620
US 1994-287066	A1	19940808
US 1995-465818	A1	19950606
WO 1995-US9056	W	19950620

AB Disclosed are methods for improving various aberrant metabolic indexes in mammals including humans by administration of muscarinic (particularly M1) receptor antagonists alone or in combination with prolactin-inhibiting compds. Preferably the administration takes place at a predetd. time (or, if a combination of muscarinic receptor antagonist and prolactin inhibitor is used, at different predetd. times) during a 24-h period when the administration is effective (or its effect more pronounced). The invention has application in the treatment of lipid and glucose metabolism disorders. The synergistic effect of methylscopolamine and bromocriptine is described.

IT **82326-74-7**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(muscarinic receptor antagonists alone or in combination with prolactin-inhibiting compds. for treatment of lipid metabolism disorders)

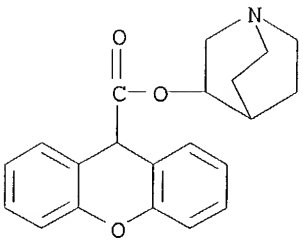
RN 82326-74-7 CAPLUS

CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

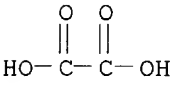
CRN 102585-08-0

CMF C21 H21 N O3



CM 2

CRN 144-62-7
CMF C2 H2 O4

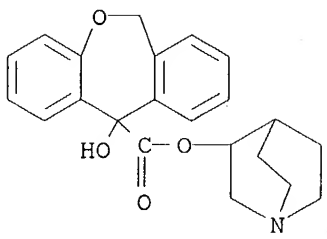


L4 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:668111 CAPLUS
DOCUMENT NUMBER: 125:316221
TITLE: Conformational analysis of anticholinergic dibenz(b, e) oxepin/thiepin hydroxycarboxylates
AUTHOR(S): Gao, Shouhai; Yun, Liuhong
CORPORATE SOURCE: Academy Military Medical Sciences, Institute Pharmacology Toxicology, Beijing, 100850, Peop. Rep. China
SOURCE: Junshi Yixue Kexueyuan Yuankan (1996), 20(2), 85-87
CODEN: JYKYEL; ISSN: 1000-5501
PUBLISHER: Junshi Yixue Kexueyuan Yuankan Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

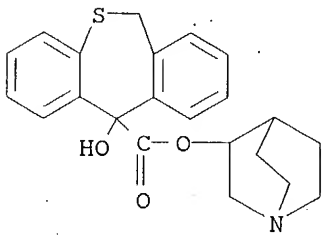
AB The low-energy conformations of 6,11-dihydro-dibenz(b, e) oxepin thiepin-11-hydroxy-11-carboxylates (I) in different configurations were obtained, and then the preferred conformation of each compound was defined through analyzing and comparing the conformational energy. The conformations of the mols. containing the piperidinic alc. were more stable when the ester bond linking to the piperidinic alc. existed as an axial bond.

IT **183560-96-5 183561-01-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(conformational anal. of anticholinergic dibenz(b, e) oxepin/thiepin hydroxycarboxylates)

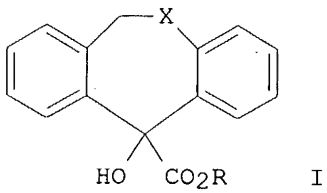
RN 183560-96-5 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



RN 183561-01-5 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:204499 CAPLUS
DOCUMENT NUMBER: 124:316966
TITLE: Synthesis and anticholinergic activities of 6,11-dihydrodibenz[b,e]oxepin and 6,11-dihydrodibenzo[b,e]thiepin hydroxycarboxylates
AUTHOR(S): Gao, Shou Hai; Yun, Liu Hong
CORPORATE SOURCE: Inst. Pharm. Toxicol., Acad. Military Med. Sci., Beijing, 100850, Peop. Rep. China
SOURCE: Chinese Chemical Letters (1996), 7(2), 115-18
CODEN: CCLEE7
PUBLISHER: Chinese Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



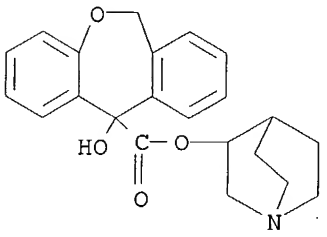
I

AB The title compds. I (R = 1-methyl-4-piperidinyl, 1-azabicyclo[2.2.2]oct-3-yl, etc., X = O, S) were synthesized by modifying the structures of xanthene compds. The pharmacol. results showed the antagonistic activities of these tricyclic compds. were all decreased at different levels after this modification, but they exhibited more selective action on the central nicotinic receptor. Especially, the compds. containing sulfur atom

almost have no action on the muscarinic receptors, they were still quite potent to the central nicotinic receptor.

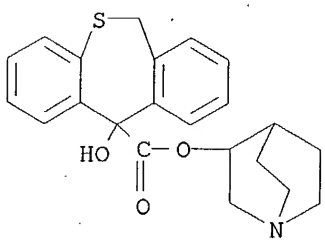
IT **176255-17-7P 176255-22-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and anticholinergic activities of 6,11-dihydrodibenz[b,e]oxepin and 6,11-dihydrodibenzo[b,e]thiepin hydroxycarboxylates)

RN 176255-17-7 CAPLUS
CN Dibenz[b,e]oxepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, 1-azabicyclo[2.2.2]oct-3-yl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 176255-22-4 CAPLUS
CN Dibenzo[b,e]thiepin-11-carboxylic acid, 6,11-dihydro-11-hydroxy-, 1-azabicyclo[2.2.2]oct-3-yl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:155536 CAPLUS
DOCUMENT NUMBER: 124:194329
TITLE: Administration of pirenzepine, methyl scopolamine and other muscarinic receptor antagonists for treatment of lipid metabolism disorders
INVENTOR(S): Cincotta, Anthony H.; Meier, Albert H.; Wilson, John M.
PATENT ASSIGNEE(S): Ergo Science Inc., USA; Board of Supervisors of Louisiana State University
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9535110	A1	19951228	WO 1995-US9056	19950620
W: AU, BR, CA, CZ, FI, HU, JP, MX, NO, NZ, SK				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5668155	A	19970916	US 1994-263607	19940620
AU 9531345	A1	19960115	AU 1995-31345	19950620
AU 702772	B2	19990304		
EP 764026	A1	19970326	EP 1995-927259	19950620
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10507159	T2	19980714	JP 1995-502626	19950620

PRIORITY APPLN. INFO.:
US 1994-263607 A 19940620
US 1988-192332 B2 19880510
US 1990-463327 B2 19900110
US 1991-719745 A2 19910624
US 1992-995292 A2 19921222
WO 1995-US9056 W 19950620

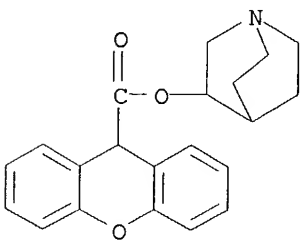
AB Disclosed are methods for improving various aberrant metabolic indexes in mammals including humans by administration of muscarinic (particularly M1) receptor antagonists alone or in combination with prolactin inhibiting compds. Preferably the administration takes place at a predetd. time (or if a combination of muscarinic receptor antagonist and prolactin inhibitor is used, at different predetd. times) during a 24-h period when the administration is effective (or its effect more pronounced). The invention has application in the treatment of lipid and glucose metabolism disorders. Oral administration of 2.5 mg/kg pirenzepine to rats decreased cholesterol plasma level to 66.10 as compared to 76.60 mg/dL for the controls.

IT **82326-74-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(muscarinic receptor antagonists for treatment of lipid metabolism disorders)

RN 82326-74-7 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

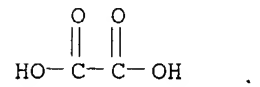
CM 1

CRN 102585-08-0
CMF C21 H21 N O3



CM 2

CRN 144-62-7
CMF C2 H2 O4



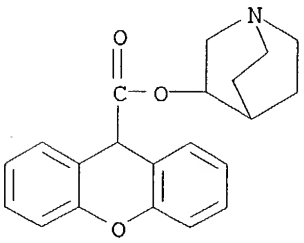
L4 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:400668 CAPLUS
DOCUMENT NUMBER: 121:668
TITLE: Muscarinic receptor selectivities of 3-quinuclidinyl 8-xanthenecarboxylate (QNX) in rat brain
AUTHOR(S): Gibson, Raymond E.; Schneidau, Timothy A.; Gitler, Mariam; Zeeberg, Barry; Reba, Richard C.
CORPORATE SOURCE: Dep. Radiol., George Washington Univ. Med. Cent., Washington, DC, 20037, USA
SOURCE: Life Sciences (1994), 54(23), 1757-65
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have determined the binding of (R)-3-Quinuclidinyl 8-xanthenecarboxylate to muscarinic acetylcholine receptor prepns. from rat cortex, hippocampus, caudate/putamen, thalamus, pons and colliculate bodies. The competition curves determined with [3H]quinuclidinyl benzilate as the radioligand are well described by a two site model with a difference in affinity between the two sites of 12-fold. The proportions of high affinity site vary from 100% in the caudate/putamen to 0% in the pons/medulla. The selectivities are different from those measured by pirenzepine and are consistent with QNX exhibiting similar affinity for the M1, M3, and M4 receptors with lower affinity for the M2 receptor. This assignment was confirmed by determining the affinities of QNX for the cloned receptor subtypes.

IT **82326-74-7**, QNX
RL: BIOL (Biological study)
(brain muscarinic receptor selectivities of)
RN 82326-74-7 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

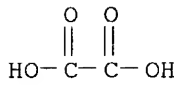
CM 1

CRN 102585-08-0
CMF C21 H21 N O3

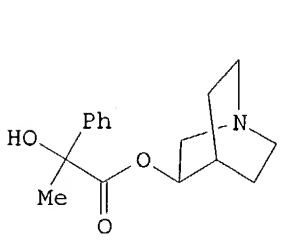


CM 2

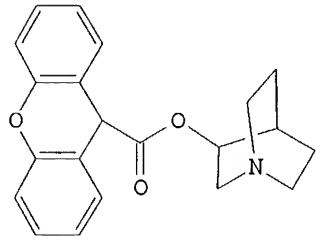
CRN 144-62-7
CMF C2 H2 O4



L4 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:144533 CAPLUS
DOCUMENT NUMBER: 116:144533
TITLE: Stereoselective antimuscarinic effects of 3-quinuclidinyl atrolactate and 3-quinuclidinyl xanthene-9-carboxylate
AUTHOR(S): Noronha-Blob, Lalita; Sturm, Bonnie; Lowe, Valerie
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, 21224, USA
SOURCE: European Journal of Pharmacology (1992), 211(1), 97-103
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



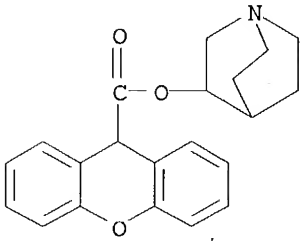
II

AB The relative affinity and selectivity of the stereoisomers of 3-quinuclidinyl atrolactate (I) and the enantiomers of 3-quinuclidinyl xanthene-9-carboxylate (II) for the pharmacol. defined muscarinic receptor subtypes was determined using functional responses of rabbit vas deferens (M1), guinea pig atria (M2) and bladder detrusor muscle (M3). All the stereoisomers behaved as competitive antagonists yielding the same rank order of potency at each receptor subtype: (RR)-I > (RS)-I > (SR)-I > (SS)-I and (R)-II > (S)-II. Moreover, the eudismic ratios relative to (RR)-I for (RS)-, (SR)- and (SS)-I, resp., ranged from 4 to 308 at all 3 subtypes. Stereoselective effects were also observed for II; (S)-II/(R)-II ratios ranged from 76 to 248. In contrast, there was a distinct lack of receptor selectivity among the isomers of I and II for either the M1, M2 or M3 muscarinic receptor subtypes. Stereoselective effects were also evident in vivo in the guinea pig cystometrogram where the rank order of potency of the isomers of I and II was similar to that observed in vitro. (RR)-I and (R)-II equipotently depressed intravesical bladder pressure (ID50=0.06 mg/kg i.v.). Other parameters (bladder capacity, threshold pressure) were unaltered by the stereoisomers. The data demonstrate that despite the high affinity of the eutomers of I and II for muscarinic receptor, they discriminate poorly among muscarinic subpopulations, thus

limiting their utility to subclassify muscarinic receptors.

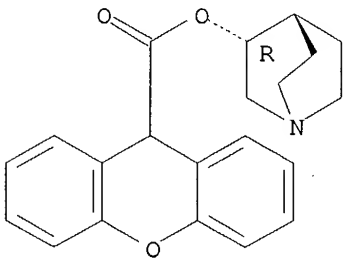
IT **102585-08-0D**, stereoisomers **114298-72-5**
114375-04-1
RL: BIOL (Biological study)
(muscarinic receptor subtypes binding by, selectivity of)

RN 102585-08-0 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



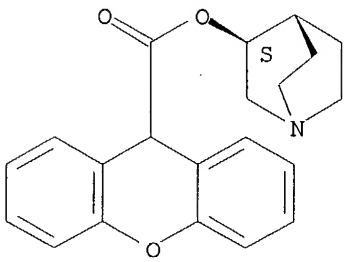
RN 114298-72-5 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 114375-04-1 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:599398 CAPLUS
DOCUMENT NUMBER: 115:199398
TITLE: Reversal of both QNX-induced locomotion and habituation decrement is indicative of M1 agonist

properties

AUTHOR(S): Carlezon, William A., Jr.; Cornfeldt, Michael L.; Szewczak, Mark R.; Fielding, Stuart; Dunn, Robert W.

CORPORATE SOURCE: Dep. Biol. Res., Hoechst-Roussel Pharm., Inc., Somerville, NJ, 08876-1258, USA

SOURCE: Drug Development Research (1991), 23(4), 333-9
CODEN: DDREDK; ISSN: 0272-4391

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Scopolamine, a non-selective muscarinic antagonist and M1 and M2 receptors, has been shown to cause hyperactivity and memory deficits in rodents. However, the relative role of activation of M1 and M2 receptors is unclear. The effects in rats of a putative M1 antagonist 3-quinuclidinyl-xanthene-9-carboxylate hemioxalate hydrate (QNX) were assessed in a paradigm that measures locomotion and habituation, a form of non-associative learning to a locomotor activity box. On day 1, s.c. administration of QNX (1.0 mg/kg) elicited a large (370%) increase in locomotion. On day 2, control animals demonstrated habituation 24 h after their first exposure to the locomotor box, as shown by decreases (-47%) in locomotor activity, while on day 2 the locomotor activity scores of animals that had been treated on the previous day with QNX did not differ from the day 1 scores of control animals. The selective M1 agonist 4-(m-chlorophenylcarbamoyloxy)-2-butynyl-trimethyl ammonium chloride (McN-A-343, 10.0 mg/kg) attenuated both the QNX-induced locomotion and habituation deficit, while neither the non-selective muscarinic agonist oxotremorine (0.125 mg/kg) nor the acetylcholinesterase inhibitor physostigmine (0.06 mg/kg) had an effect on these behaviors. These data suggest that, in this model, the M1 cholinergic receptor mediates both locomotion and habituation. Furthermore, M1 agonists can be identified by reversal of both QNX-induced locomotion and memory decrement in this paradigm.

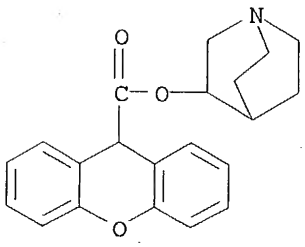
IT **82326-74-7**, QNX
RL: BIOL (Biological study)
(habituation and locomotor behaviors response to, muscarinic M1 receptor role in)

RN 82326-74-7 CAPLUS

CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

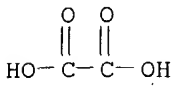
CM 1

CRN 102585-08-0
CMF C21 H21 N O3



CM 2

CRN 144-62-7
CMF C2 H2 O4



L4 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:240518 CAPLUS
DOCUMENT NUMBER: 114:240518
TITLE: Effects of cyproheptadine and pizotifen on central muscarinic receptors
AUTHOR(S): Richards, Mary H.
CORPORATE SOURCE: Marion Merrell Dow Res. Inst., Strasbourg, 67084, Fr.
SOURCE: European Journal of Pharmacology (1991), 195(3), 403-5
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

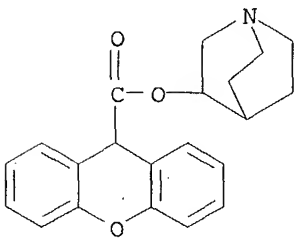
AB The affinities of cyproheptadine, pizotifen and (±)-quinuclidinyl xanthane-9-carboxylate hemioxylate (QNX) were determined at muscarinic autoreceptors and postsynaptic (IP1 formation) receptors in rat hippocampal slices. The affinity values for QNX were 8.2 and 8.5 resp. Cyproheptadine and pizotifen were less potent than QNX. Pizotifen was slightly (2-fold) less active at antagonizing IP1 formation than blocking the autoreceptors whereas cyproheptadine was equally active at antagonizing the two hippocampal muscarinic receptors.

IT **82326-74-7**, QNX
RL: PRP (Properties)
(muscarinic receptor affinity of, at autoreceptors and postsynaptic receptors in hippocampus)

RN 82326-74-7 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

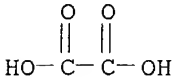
CM 1

CRN 102585-08-0
CMF C21 H21 N O3



CM 2

CRN 144-62-7
CMF C2 H2 O4

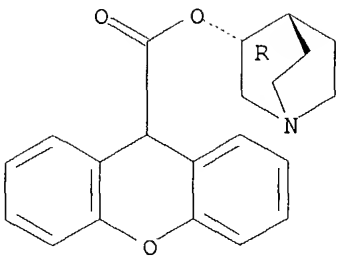


L4 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:624907 CAPLUS
DOCUMENT NUMBER: 113:224907
TITLE: Specificity of methoctramine in blocking muscarinic receptors which inhibit adenylate cyclase in cerebellar granule cells
AUTHOR(S): McLeskey, Sandra W.; Fischofer-Hahn, Carol; Takahashi, K.; Wojcik, W. J.
CORPORATE SOURCE: Sch. Med., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Neuropharmacology (1990), 29(9), 853-60
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In primary cultures of cerebellar granule cells, activation of muscarinic receptors stimulates both hydrolysis of phosphatidylinositol (PI) and inhibition of adenylate cyclase. The specificity of 3 muscarinic receptor antagonists, pirenzepine, methoctramine, and (-)quinuclidinyl xanthene-9-carboxylate [(-)QNX], in blocking carbachol-stimulated hydrolysis of PI and inhibition of adenylate cyclase were determined Pirenzepine was found nonspecific in blocking the carbachol-stimulated hydrolysis of PI and inhibition of adenylate cyclase, while methoctramine specifically antagonized carbachol-stimulated inhibition of adenylate cyclase with 600 times greater potency than carbachol-stimulated hydrolysis of PI. (-)QNX was approx. 20 times more potent in blocking the carbachol-stimulated hydrolysis of PI than inhibition of adenylate cyclase. In studies of the ability of these 3 antagonists to block the binding of [3H]quinuclidinyl benzilate ([3H]QNB) to muscarinic sites on membranes from cerebellar granule cells, all 3 antagonists displayed binding characteristics indicative of 2 binding sites, possibly representing the 2 types of muscarinic receptors. However, the ratio of the affinities for each of the 2 binding sites was about 10 for pirenzepine, 100 for methoctramine, and 650 for (-)QNX. Thus, the specificity of these antagonists, in blocking the inhibition of adenylate cyclase and hydrolysis of PI did not correlate with their specificities obtained with the binding studies with [3H]QNB. Since 4 or possibly 5 muscarinic receptive proteins have been described, it is possible that this discrepancy can be explained by the high affinity binding of each antagonist to a different subset of muscarinic receptive proteins, some of which are coupled to receptors stimulating the hydrolysis of PI and some to receptors inhibiting adenylate cyclase. Methoctramine seems specific for those muscarinic receptive proteins coupled to the inhibition of adenylate cyclase.

IT **114298-72-5**
RL: BIOL (Biological study)
(adenylate cyclase inhibition and phosphatidylinositol hydrolysis response to muscarinic activation in cerebellum antagonism by)
RN 114298-72-5 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)- (9CI) (CA INDEX NAME)

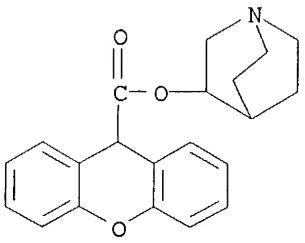
Absolute stereochemistry.



L4 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:586915 CAPLUS
DOCUMENT NUMBER: 111:186915
TITLE: Selective muscarinic antagonists free of hallucinogenic properties. Parts A and B
AUTHOR(S): Rzeszotarski, W. J.; Cohen, V. I.; Grimm, L. J.; Rothblat, L. A.
CORPORATE SOURCE: ORINCON Corp., La Jolla, CA, USA
SOURCE: Report (1986), Order No. AD-A203344, 36 pp. Avail.: NTIS
From: Gov. Rep. Announce. Index (U. S.) 1989, 89(10), Abstr. No. 926,630
DOCUMENT TYPE: Report
LANGUAGE: English

AB A highly potent psychotomimetic drug 3-quinuclidinyl benzylilate (QNB) with antimuscarinic properties, which has been proven useful in the study of brain muscarinic receptor was synthesize. With the use of (3H)-QNB an effort was undertaken to correlate the relative binding affinities of various anticholinergic agents with their anticholinergic and psychomimetic efficacy. In the study on structure activity relationship, the analogs of QNB were synthesized and their pharmacol. properties reported. The affinities of atropine, scopolamine, 3-quinuclidinol benzilate and its analogs were determined for the muscarinic acetylcholine receptor using membrane prepns. from caudate putamen and ventricular muscle. Two of these compds., 3-quinuclidinylatrolactate (QNA) and 3-quinuclidinyl xanthene-9-carboxylate (QNX) exhibited greater affinity for the M1-receptor. QNX has the same affinity for the M1-receptor as QNB and M1-selectivity comparable to that of pirenzepine. Like atropine, QNX and QNA produce hallucinations. In an effort to improve the selective activity and eliminate hallucinogenic properties, the authors have decided to synthesize and resolve optical isomers of 3-quinuclidinyl atrolactate, chromane-4-carboxylate and xanthene-9-carboxylate which have a selective affinity for the M-1 receptor when compared to QNB.

IT **102585-08-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and muscarinic receptor affinity and pharmacol. of)
RN 102585-08-0 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)

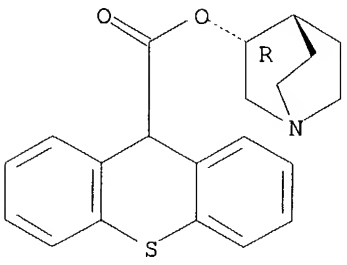


L4 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:451076 CAPLUS
DOCUMENT NUMBER: 111:51076
TITLE: Muscarinic receptors: relationships among phosphoinositide breakdown, adenylate cyclase inhibition, in vitro detrusor muscle contractions and in vivo cystometrogram studies in guinea pig bladder
AUTHOR(S): Noronha-Blob, L.; Lowe, V.; Patton, A.; Canning, B.; Costello, D.; Kinnier, W. J.
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1989), 249(3), 843-51
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relations between activation of muscarinic receptors in guinea pig bladder, measured as carbachol-stimulated inositol phosphate (IP) accumulation, oxotremorine-induced adenylate cyclase (AC) inhibition and bladder detrusor smooth muscle contraction determined in vitro as well as in vivo in the slow filling cystometrogram (CMG), were analyzed from the potencies of a number of muscarinic antagonists to block these responses. Pos. linear correlations were found among the inhibitory potencies of 10 muscarinic antagonists to inhibit phosphoinositide (PI) turnover and detrusor muscle contraction in vitro, as well as peak intravesical bladder pressure in vivo in the CMG. In contrast, there was no correlation between the potency of antagonists to block the AC inhibitory response and either in vitro or in vivo guinea pig bladder contractions. Muscarinic agonists inhibited basal AC activity to a maximum of 20% in a GTP-dependent, Na+-sensitive manner and dose dependently stimulated both PI breakdown (3-4-fold) and isolated detrusor contractions. Again, a correlation was calculated among the potencies of 7 muscarinic agonists to elicit PI turnover and in vitro muscle contraction, whereas no correlation was observed between their potencies to inhibit AC activity and contractile responses in vitro. Evidently, IP accumulation and presumably IP-induced Ca2+ release may function as the transducing mechanism for cholinergic contraction of the urinary bladder. Also, inasmuch as pirenzepine and AF-DX 116 were among the least potent inhibitors of PI stimulation, AC inhibition, and detrusor muscle contraction both in vitro and in vivo in the CMG, it appears that M2 receptors distinct from the cardiac M2 subtype are involved in bladder function.

IT **112605-31-9**, (R)-QNX
RL: BIOL (Biological study)
(adenylate cyclase inhibition and bladder muscle contraction and phosphoinositide hydrolysis prevention by, in bladder, interrelations of)
RN 112605-31-9 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



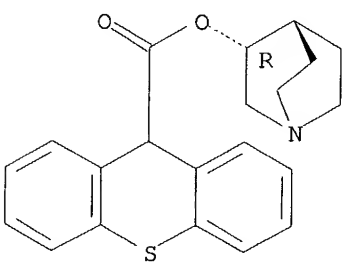
L4 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:653 CAPLUS
DOCUMENT NUMBER: 110:653
TITLE: Selective agents for muscarinic receptors linked to phosphoinositide breakdown
AUTHOR(S): Noronha-Blob, Lalita; Canning, Brendan; Costello, Diane; Kinnier, William J.
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, 21224-2788, USA
SOURCE: European Journal of Pharmacology (1988), 154(2), 161-7
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of several muscarinic agonists and antagonists were examined on phosphoinositide breakdown (PI) and adenylate cyclase (AC) inhibition in rat cerebral cortex and heart, resp. Acetylcholine, carbachol, and methacholine behaved as full agonists in both systems. In contrast, oxotremorine and arecoline failed to stimulate PI turnover but were potent and efficacious at inhibiting AC. Among the antagonists, pirenzepine, dicyclomine, telenzepine, and (R)-QNA were both potent (Ki .apprx. 0.5-7.5 nM) and selective (90-8500-fold) for the PI-linked (putatively M1) brain receptor. In contrast, the cardioselective and ileal-selective M2 antagonists, AF-DX 116 and hexahydrosiladifenidol, were equipotent, competitive inhibitors of both responses. The selectivity of these drugs in terms of their biochem. responses is described.

IT **112605-31-9**
RL: BIOL (Biological study)
(adenyl cyclase of heart and phosphoinositide metabolism in brain response to)

RN 112605-31-9 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:416578 CAPLUS
DOCUMENT NUMBER: 109:16578
TITLE: Affinity and selectivity of the optical isomers of 3-quinuclidinyl benzilate and related muscarinic antagonists
AUTHOR(S): Rzeszotarski, W. Janusz; McPherson, Daniel W.; Ferkany, John W.; Kinnier, William J.; Noronha-Blob, Lalita; Kirkien-Rzeszotarski, Alicja
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, 21224-2788, USA
SOURCE: Journal of Medicinal Chemistry (1988), 31(7), 1463-6
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB All of the optical isomers of the muscarinic antagonists 3-quinuclidinyl benzilate (QNB), 3-quinuclidinyl xanthene-9-carboxylate (QNX), and 3-quinuclidinyl atrolactate (QNA) were prepared and studied in binding and functional assays. In all instances, the esters of (R)-3-quinulcidinol had greater affinity for the M1 and M2 subpopulations of muscarinic acetylcholine receptors (M-AChRs) than did their S counterparts. The enantiomers of QNB, QNX, and QNA in which the alc. portion of the muscarinic antagonists had the S absolute stereochem. were more selective for the M1-AChRs. This selectivity was modulated by the nature and, in the case of QNA, the chirality of the acid portion. The most potent isomer in the series was (R)-QNB. In the QNA series the diastereoisomer with the absolute R configuration of the alc. (a) and the R configuration of the acid (b) was the most potent in both binding and functional assays whereas (Sa, Rb)-QNA was the most selective for the M1 subtype of M-AChRs. In fact, the latter diastereomer was as potent and selective as pirenzepine for M1-AChRs.

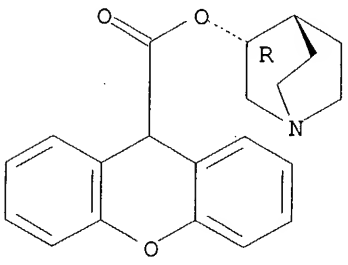
IT **114298-73-6P 114375-05-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and muscarinic receptor-binding and antimuscarinic activities of)

RN 114298-73-6 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

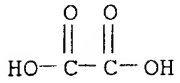
CRN 114298-72-5
CMF C21 H21 N O3

Absolute stereochemistry.



CM 2

CRN 144-62-7
CMF C2 H2 O4

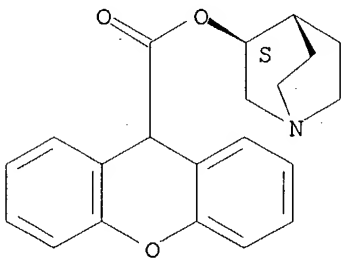


RN 114375-05-2 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (S)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

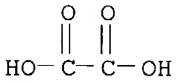
CRN 114375-04-1
CMF C21 H21 N O3

Absolute stereochemistry.

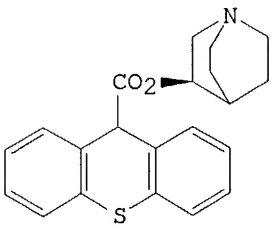


CM 2

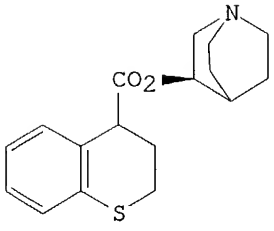
CRN 144-62-7
CMF C2 H2 O4



L4 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:124047 CAPLUS
DOCUMENT NUMBER: 108:124047
TITLE: Synthesis and structure-activity relationships of new muscarinic antagonists
AUTHOR(S): Cohen, Victor I.; Gibson, Raymond E.; Reba, Richard C.
CORPORATE SOURCE: Sect. Radiopharm. Chem., George Washington Univ. Med. Cent., Washington, DC, 20037, USA
SOURCE: Journal of Pharmaceutical Sciences (1987), 76(10), 848-50
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 108:124047
GI



I



II

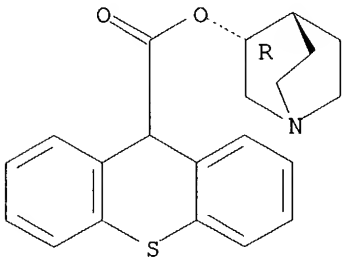
AB In an attempt to develop more selective muscarinic acetylcholine receptor antagonists, (R)-1-azabicyclo[2.2.2]oct-3-yl-thioxanthene-9-carboxylate, (RS)-thiochromane-4-carboxylate, and (RS)-chromane-4-carboxylate were synthesized. Evaluation of the binding affinities of these compds. to muscarinic receptors of dog heart and rat striatum indicated that replacing the O by S in the xanthenyl and chromanyl moieties did not change selectivity, but reduced the affinity of I compound and enhanced the affinity of II.

IT **112605-31-9P**, (R)-3-Quinuclidinyl thioxanthene-9-carboxylate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and muscarinic antagonist activity of, structure in relation to)

RN 112605-31-9 CAPLUS

CN 9H-Thioxanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:512 CAPLUS

DOCUMENT NUMBER: 108:512

TITLE: Comparison of in vitro actions with behavioral effects of antimuscarinic agents

AUTHOR(S): Witkin, J. M.; Gordon, R. K.; Chiang, P. K.

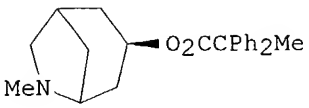
CORPORATE SOURCE: Dep. Med. Neurosci., Walter Reed Army Inst. Res., Washington, DC, 20307-5100, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 242(3), 796-803
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



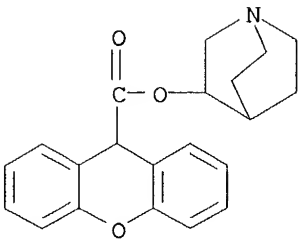
I

AB In vitro potencies of a series of muscarinic antagonists were compared with their effects on operant behavior. Ki Values for inhibition of [3H]N-methylscopolamine binding in N4TG1 neuroblastoma cells correlated pos. with ED50 values for the inhibition of carbachol-induced α-amylase release from pancreatic acini cells and with KB values for inhibition of acetylcholine-induced contractions of guinea pig ileum. The rank order of potency for inhibition of [3H]N-methylscopolamine binding was quinuclidinyl benzilate = quinuclidinyl xanthene-9-carboxylate > (Me atropine = atropine) > benactyzine > azaprophen (I) > (adiphenine = aprophen) > pirenzepine > Et aprophen. The M1 antagonist, pirenzepine, was a weak inhibitor in the guinea pig ileum and α-amylase assays relative to its ability to inhibit [3H]N-methylscopolamine binding; azaprophen exhibited the opposite relationship. Lever-press responses of rats were maintained by food delivery under a schedule requiring 10 responses for each food presentation. The high response rates engendered by this schedule were decreased in a dose-dependent manner by all compds. The order of potency for this behavioral effect (ED50) was atropine-azaprophen > aprophen > (Me atropine = benactyzine) > pirenzepine > adiphenine. Behavioral depressant actions of the antimuscarinics correlated pos. with their potencies in inhibiting α-amylase secretion. Pirenzepine was unique in being relatively more potent in its behavioral effects than in its action in vitro. In contrast to the other antimuscarinic agents studied, the benzilates, benactyzine, aprophen and adiphenine, but not azaprophen, increased behavioral response rates. Nevertheless, dose-response functions for the behavioral effects of oxotremorine were shifted 3-fold to the right by either atropine or aprophen. These results indicate that 1) a population of muscarinic receptors with properties like those of pancreatic acini cells may be relevant to the behavioral depressant effects of the antimuscarinic compds. studied, 2) the behavioral excitatory effects of antimuscarinic agents are not a general consequence of muscarinic receptor blockade and 3) the pharmacol. profiles of azaprophen and pirenzepine are unique among the antimuscarinics studied; azaprophen may interact with a subset of muscarinic receptors distinct from those preferred by pirenzepine. Compds. like azaprophen may be effective antimuscarinic agents in vivo at doses that do not produce the undesirable behavioral effects found with existing centrally active antimuscarinic compds.

IT **102585-08-0**
RL: PRP (Properties)
(behavioral effects of, in vitro pharmacol. in)

RN 102585-08-0 CAPLUS

CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



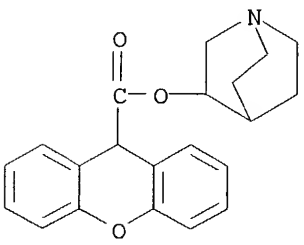
L4 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:547172 CAPLUS
DOCUMENT NUMBER: 107:147172
TITLE: Selectivity of muscarinic antagonists in radioligand and in vivo experiments for the putative M1, M2 and M3 receptors
AUTHOR(S): Doods, Henri N.; Mathy, Marie Jeanne; Davidesko, David; Van Charldorp, Karin J.; De Jonge, Adriaan; Van Zwieten, Pieter A.
CORPORATE SOURCE: Div. Pharmacother., Univ. Amsterdam, Amsterdam, 1018 TV, Neth.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 242(1), 257-62
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of the muscarinic receptors present in the hippocampus, sympathetic ganglia, atria, and salivary glands of the rat was examd both in vivo and in radioligand binding expts. . It is proposed that there are 3 different binding sites present in hippocampal, atrial, and submandibular membranes and it is proposed that these be classified as M1, M2 and M3, resp. Both in vivo and in vitro pirenzepine appears to possess high affinity for M1 receptors, whereas 4-diphenylacetoxy-N-methylpiperidine methobromide and dicyclomine show high affinity for both M1 and M3 receptors. AF-DX 116 displayed high affinity for M2 receptors.

IT **82326-74-7**
RL: BIOL (Biological study)
(muscarinic receptor-antagonist activity of, selectivity of)
RN 82326-74-7 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

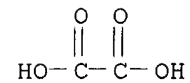
CM 1

CRN 102585-08-0
CMF C21 H21 N O3



CM 2

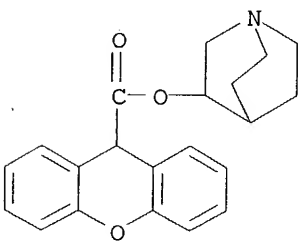
CRN 144-62-7
CMF C2 H2 O4



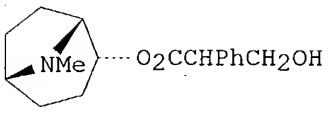
L4 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1984:435215 CAPLUS
DOCUMENT NUMBER: 101:35215
TITLE: In vivo competition studies with analogs of 3-quinuclidinyl benzilate
AUTHOR(S): Eckelman, William C.; Grissom, M.; Conklin, J.; Rzeszotarski, W. J.; Gibson, R. E.; Francis, B. E.; Jagoda, E. M.; Eng, R.; Reba, R. C.
CORPORATE SOURCE: Med. Cent., George Washington Univ., Washington, DC, 20037, USA
SOURCE: Journal of Pharmaceutical Sciences (1984), 73(4), 529-34
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Among ligands that bind to the α and β-adrenoceptors and to the muscarinic acetylcholine receptor (m-AChR), those that bind to the latter have the best properties for external detection of receptor sites by γ-camera imaging. To develop the optimal radiotracer, nonradioactive analogs of 3-quinuclidinyl benzilate (I) were tested in in vivo in male Sprague-Dawley rats displacement studies with (-)-[3H]-I to determine their ability to compete with (-)-[3H]-I for the muscarinic acetylcholine receptor. There is a linear correlation between the ability to compete with (-)-[3H]-I for the m-AChR and the affinity constant of the analog as determined by in vitro assay, suggesting that the test is a valid indicator of in vivo distribution. One radioiodinated analog, 3-quinuclidinyl p-iodobenzilate, bound to m-AChR in the heart and brain of rats.

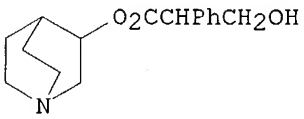
IT **102585-08-0**
RL: PROC (Process)
(binding of, to adreno- and muscarinic acetylcholine receptors)
RN 102585-08-0 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



L4 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1983:587523 CAPLUS
DOCUMENT NUMBER: 99:187523
TITLE: Parasympatholytic (anticholinergic) esters of the isomeric 2-tropanols. 2. Non-glycolates
AUTHOR(S): Atkinson, Edward R.; McRitchie-Ticknor, Donna D.; Harris, Louis S.; Archer, Sydney; Aceto, Mario D.; Pearl, J.; Luduena, F. P.
CORPORATE SOURCE: Arthur D. Little, Inc., Cambridge, MA, 02140, USA
SOURCE: Journal of Medicinal Chemistry (1983), 26(12), 1772-5
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

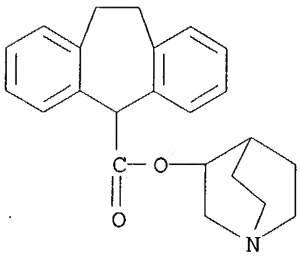


II

AB Nineteen nonglycolate esters of (+)-2α- and (-)-2β-tropanol and (±)-3-quinuclidinol, 16 of which were prepared by known smaller-scale transesterification, were evaluated for their central and peripheral activities and compared with the known glycolate esters. (+)-2α-Tropanyl (±)-tropate (I) [87421-55-4] and (±)-3-quinuclidinyl (±)-tropate (II) [87395-64-0] were approx. equivalent to one another and to the reference compound atropine. (+)-2α-Tropanyl fluorodiphenylacetate [87421-57-6] and (±)-3-quinuclidinyl fluorodiphenylacetate [87395-66-2] had approx. equal peripheral activity. The remaining compds. were relatively inactive.

IT **87395-65-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(parasympatholytic activity of)

RN 87395-65-1 CAPLUS
CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



L4 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1983:498823 CAPLUS
DOCUMENT NUMBER: 99:98823
TITLE: Differences in affinities of muscarinic acetylcholine receptor antagonists for brain and heart receptors

AUTHOR(S): Gibson, Raymond E.; Rzeszotarski, Waclaw J.; Eckelman, William C.; Jagoda, Elaine M.; Weckstein, Douglas J.; Reba, Richard C.
CORPORATE SOURCE: Med. Cent., George Washington Univ., Washington, DC, 20037, USA
SOURCE: Biochemical Pharmacology (1983), 32(12), 1851-6
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
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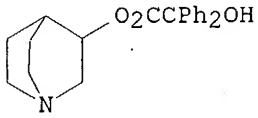
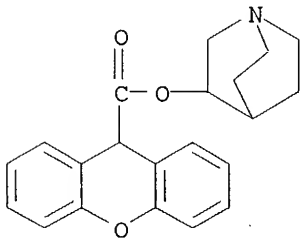


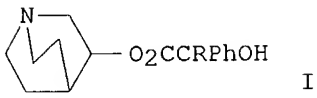
I

AB The affinities of atropine [51-55-8], scopolamine [51-34-3], 3-quinuclidinyl benzilate (I) [4478-53-9] and 12 analogs of 3-quinuclidinyl benzilate were determined for the muscarinic acetylcholine receptor (m-AChR) using membrane prepns. from caudate/putamen. The affinity consts. thus obtained were compared with affinities previously reported for the m-AChR obtained from ventricular muscle. The affinities differed significantly for 6 of the compds., the largest difference being 16-fold. Neither solubilization nor variation of physiol. significant salts led to a significant change in the affinity of that compound These results are interpreted as supporting the subclassification of the muscarinic acetylcholine receptor.
IT **102585-08-0**
RL: PROC (Process)
(binding of, by muscarinic receptors of brain and heart, structure in relation to)
RN 102585-08-0 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



L4 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1982:465990 CAPLUS
DOCUMENT NUMBER: 97:65990
TITLE: Analogs of 3-quinuclidinyl benzilate
AUTHOR(S): Rzeszotarski, W. J.; Gibson, R. E.; Eckelman, W. C.; Simms, D. A.; Jagoda, E. M.; Ferreira, N. L.; Reba, R. C.
CORPORATE SOURCE: Med. Cent., George Washington Univ., Washington, DC, 20037, USA
SOURCE: Journal of Medicinal Chemistry (1982), 25(9), 1103-6

CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

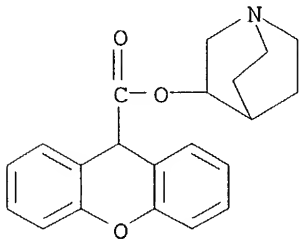
AB Twelve 3-quinuclidinyl benzilate analogs I (R = Br, substituted Ph, etc.) were synthesized and their affinities to muscarinic receptors from rat or dog ventricular muscle were measured. The muscarinic receptor can to different degrees accommodate either a halogen in the ortho, meta, or para position of 1 Ph ring or the replacement of 1 Ph ring with an alkyl group. The affinities lie within a 270-fold range: the highest affinity compound 3-quinuclidinyl α-hydroxy-α-cyclopentylphenylacetate hemioxalate [82326-63-4] to the lowest affinity compound, 3-quinuclidinyl α-hydroxy-α-2-propargylphenylacetate oxalate [82326-72-5].

IT **82326-74-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and muscarinic receptor binding by, structure in relation to)

RN 82326-74-7 CAPLUS
CN 9H-Xanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester, ethanedioate (1:1) (9CI) (CA INDEX NAME)

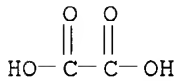
CM 1

CRN 102585-08-0
CMF C21 H21 N O3



CM 2

CRN 144-62-7
CMF C2 H2 O4



L4 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1971:13022 CAPLUS
DOCUMENT NUMBER: 74:13022

10/740,264

TITLE: Cholinolytic quinuclidinol derivatives
PATENT ASSIGNEE(S): Societe Generale de Recherches et d'Applications Scientifiques "Sogeras"
SOURCE: Fr. Demande, 30 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2012964		19700327		
GB 1219606			GB	

PRIORITY APPLN. INFO.: GB 19680715

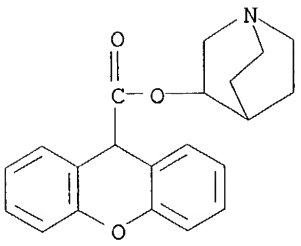
GI For diagram(s), see printed CA Issue.

AB C4H3S = thienyl and C6H11 = cyclohexyl in this abstract The title compds., (I) (R = H, OH, or alkyl; R1 = Ph or C4H3S; R2 = C6H11, cyclopentyl, or C4H3S) and II, are prepared when R = H or alkyl, by the reaction of an acid chloride, RR1R2CCOCl with 3-quinuclidinol, and when R = OH by transesterification of quinuclidinol by an ester R1R2C(OH)CO2R3, where R3 = Me or Et. Thus, 0.54 g NaOMe in 160 ml anhydrous heptane treated with 13.2 g Me 2-cyclohexyl-2-hydroxy-2-phenylethanoate and 11.6 g 3-quinuclidinol and the mixture refluxed 4 hr under a Dean-Stark head to eliminate MeOH gave a diastereomeric mixture of I (R = OH, R1 = C6H11, R2 = Ph), m. 98-100°. Similarly prepared were I (R, R1, and R2 given): OH, Ph, cyclopentyl; OH, Ph, C4H3S; OH, cyclopentyl, C4H3S; OH, C4H3S, C4H3S. These compds. were characterized by their methobromides. C6H11PhCHCO2H (5 g) refluxed 2 hr in 25 ml SOCl2 yielded 5.4 g C6H11PhCHCOCl. The acid chloride in 20 ml C6H6 added to 3.4 g Na derivative of 3-quinuclidinol in 50 ml C6H6 and the mixture refluxed 2.5 hr the oily I (R = H, R1 = Ph, R2 = C6H11) (III) treated in hot EtOAc with maleic acid gave III acid maleate. Similarly prepared were I (R = Me, R1 = R2 = C4H3S), characterized as the methobromide and I (R = H, R1 = Ph, R2 = C4H3S), converted to the acid oxalate. SOCl2 (20 ml) and 25 g 9-carboxyxanthene in 90 ml CCl4 refluxed 2.5 hr and the mixture evaporated at 40° in vacuo, the acid chloride recovered from C6H6 and refluxed with 19.1 g 3-quinuclidinol in 800 ml dry C6H6, the cold solution treated with 800 ml H2O, 70 ml 10N NaOH and 35 g K2CO below 7° and worked up gave 3-(9-xanthenylcarboxy)quinuclidine-HCl, converted to the corresonding methobromide. Similarly prepared were 3-(9,10-dihydro-9-anthracenylcarboxy)quinuclidine methobromide and ethobromide) and 3-(9-thioxanthenylcarboxy)-quinuclidine (methobromide). The compds. show spasmolytic and anticholinergic activity 0.5-50 times that of an equivalent dose of atropine sulfate.

IT **29125-63-1P 29125-64-2P 29125-65-3P**
29125-66-4P 29125-67-5P 29125-68-6P
29125-69-7P 29125-70-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

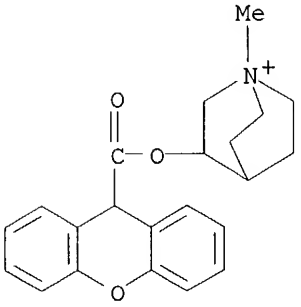
RN 29125-63-1 CAPLUS

CN Xanthene-9-carboxylic acid, 3-quinuclidinyl ester hydrochloride (8CI) (CA INDEX NAME)



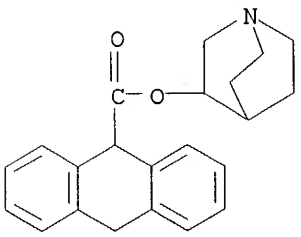
● HCl

RN 29125-64-2 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)

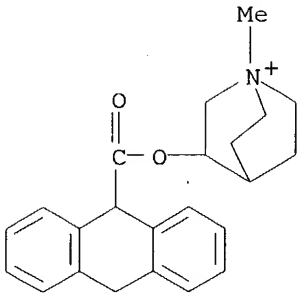


● Br^-

RN 29125-65-3 CAPLUS
CN 9-Anthroic acid, 9,10-dihydro-, 3-quinuclidinyl ester (8CI) (CA INDEX NAME)

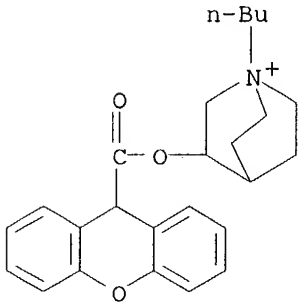


RN 29125-66-4 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, 9,10-dihydro-9-anthroate (8CI) (CA INDEX NAME)



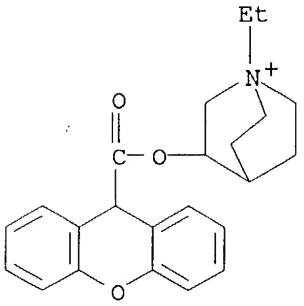
● Br^-

RN 29125-67-5 CAPLUS
CN Quinuclidinium, 1-butyl-3-hydroxy-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)



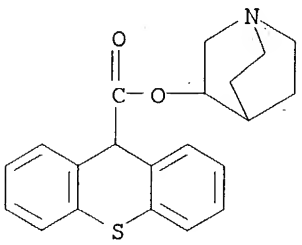
● Br^-

RN 29125-68-6 CAPLUS
CN Quinuclidinium, 1-ethyl-3-hydroxy-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)

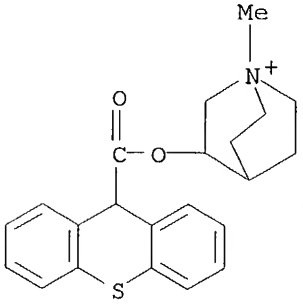


● Br^-

RN 29125-69-7 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



RN 29125-70-0 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, thioxanthene-9-carboxylate (8CI) (CA INDEX NAME)

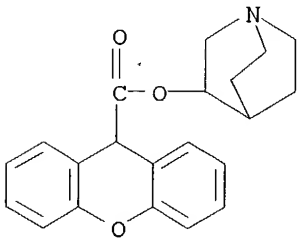


● Br^-

L4 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1970:520520 CAPLUS
DOCUMENT NUMBER: 73:120520
TITLE: Quinuclidinol derivatives and their use in preparing drugs
INVENTOR(S): Labey, Robert; Gueremy, Claude; Thevenot, Roger
PATENT ASSIGNEE(S): Societe Generale de Recherches et d'Applications Scientifiques "Sogeras"
SOURCE: Ger. Offen., 44 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

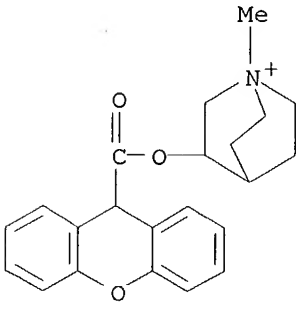
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 1935751	A	19700226	DE 1969-1935751	19690714
GB 1233459	A	19710526	GB 1968-33564	19680715
US 3609686	A	19710928	US 1969-840319	19690709
SE 361315	B	19731029	SE 1972-9351	19690714

US 3714357 A 19730130 US 1969-841970 19690715
PRIORITY APPLN. INFO.: GB 1968-33564 19680715
GI For diagram(s), see printed CA Issue.
AB Anticholinergic quinuclidinols were prepared Thus, a mixture of Me α-cyclohexyl-α-hydroxyphenylacetate, 3-quinuclidinol, and NaOMe in heptane, was refluxed 4 hr to give I, m. 143° (CH3CN). Treatment of I with 2M methanolic MeBr gave I.MeBr, m. 160°. Similarly prepared were 15 other compds.
IT **29125-63-1P 29125-64-2P 29125-65-3P**
29125-66-4P 29125-67-5P 29125-68-6P
29125-69-7P 29125-70-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 29125-63-1 CAPLUS
CN Xanthene-9-carboxylic acid, 3-quinuclidinyl ester hydrochloride (8CI) (CA INDEX NAME)



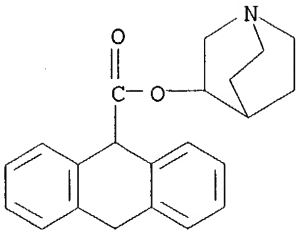
● HCl

RN 29125-64-2 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)

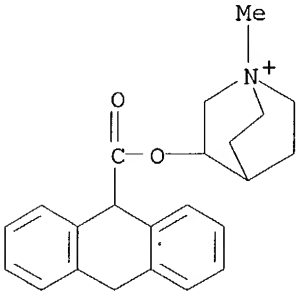


● Br^-

RN 29125-65-3 CAPLUS
CN 9-Anthroic acid, 9,10-dihydro-, 3-quinuclidinyl ester (8CI) (CA INDEX NAME)

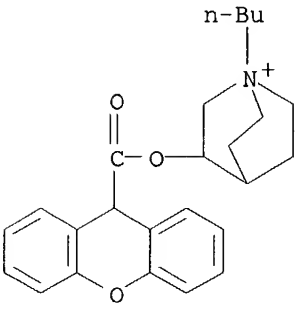


RN 29125-66-4 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, 9,10-dihydro-9-anthroate (8CI) (CA INDEX NAME)



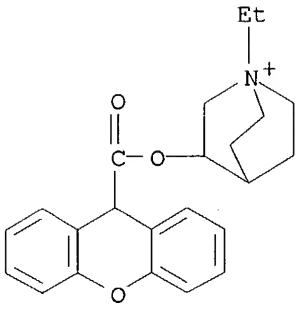
● Br^-

RN 29125-67-5 CAPLUS
CN Quinuclidinium, 1-butyl-3-hydroxy-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)



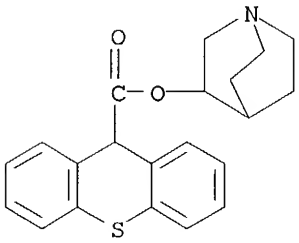
● Br^-

RN 29125-68-6 CAPLUS
CN Quinuclidinium, 1-ethyl-3-hydroxy-, bromide, xanthene-9-carboxylate (8CI) (CA INDEX NAME)

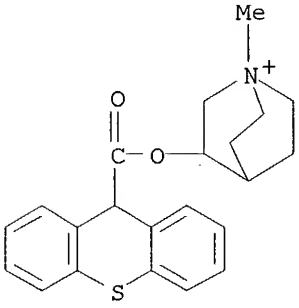


● Br^-

RN 29125-69-7 CAPLUS
CN 9H-Thioxanthene-9-carboxylic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



RN 29125-70-0 CAPLUS
CN Quinuclidinium, 3-hydroxy-1-methyl-, bromide, thioxanthene-9-carboxylate (8CI) (CA INDEX NAME)



● Br^-

L4 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1966:482198 CAPLUS
DOCUMENT NUMBER: 65:82198
ORIGINAL REFERENCE NO.: 65:15352d-h

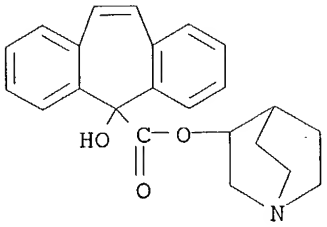
TITLE: Therapeutic 5-hydroxy-5H-dibenzo [a,d] cycloheptene-5-carboxylates
PATENT ASSIGNEE(S): N. V. Koninklijke Pharmaceutische Fabrieken voorheen Brocades-Stheeman & Pharmacia
SOURCE: 11 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
NL 6513732		19660502	NL	
PRIORITY APPLN. INFO.:			GB	19641031

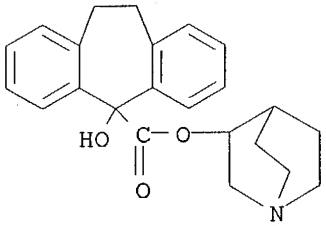
GI For diagram(s), see printed CA Issue.

AB Title compds. of the general formulas I and II, where R is 3-quinuclidinyl or 3-tropanyl, were prepared by transesterification of the corresponding methyl ester (III) with 3-quinuclidinol (IV) or tropine in C6H6, in the presence of NaH. The free acids of I and II, used to prepare the starting III, were prepared by treating the corresponding 5H-dibenzo[a,d]cyclohepten-5-one with Na and CO2 in dioxane. Thus, a mixture of 500 cc. anhydrous dioxane and 47 g. Na was refluxed until Na melted, and another 250 cc. anhydrous dioxane was added with vigorous stirring. The mixture was cooled to room temperature and 200 g. 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one was added at a temperature below 20°. CO2 was added together with 500 cc. tetrahydrofuran until the blue color disappeared, solid CO2 and water were added until the solid material dissolved, the clear solution was concentrated at reduced pressure to approx. half its volume and extracted with Et2O, and the aqueous phase was acidified with 2N HCl to precipitate 90% 5-hydroxy-10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5-carboxylic acid (V), m. 170-90°. Diazomethane was added to V in Et2O until the yellow color persisted and the excess diazomethane decomposed by adding AcOH. The solution was washed with dilute NaHCO3 and water, dried on Na2SO4, and filtered, and the solvent distilled to give 90% of the corresponding III (VI) m. 138-40° (CCl4). VI (13 g.) and 0.4 g. a 50% suspension of NaH in a mineral oil were added carefully to 15 g. IV in 60 cc. anhydrous C6H6, and the azeotropically distilled water-C6H6 mixture was replaced by anhydrous C6H6 during 4 hrs. The mixture was cooled, the NaH decomposed by adding 20 cc. water and the C6H6 phase washed with water and treated with Et2O and petr. ether (b. 28-40°). The precipitate was filtered off and washed with water and Et2O and the combined organic phases were treated with dilute HCl and alkalized to give another precipitate which was added to the former, the total yield being 89% I (R = 3-quinuclidinyl), m. 204-6° (dioxane). Similarly prepared were 30% I (R = 3-tropanyl), m. 200-2°, 66% II (R = 3-quinuclidinyl), m. 257-9°, and 30% II (R = 3-tropanyl), m. 248-50°. I and II are used as antiarythmetic and atropine-like agents.

IT **10541-17-0**, 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 5-hydroxy-, 3-quinuclidinyl ester **10541-19-2**, 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-5-hydroxy-, 3-quinuclidinyl ester
(preparation of)
RN 10541-17-0 CAPLUS
CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 5-hydroxy-, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



RN 10541-19-2 CAPLUS
CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-5-hydroxy-, 3-quinuclidinyl ester (7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1966:59707 CAPLUS
DOCUMENT NUMBER: 64:59707
ORIGINAL REFERENCE NO.: 64:11141h,11142a-h,11143a-c
TITLE: Experiments in the 5H-dibenzo[a,d]cycloheptene series. II. Synthesis of some esters and piperazine derivatives of 5H-dibenzo[a,d]cycloheptene
AUTHOR(S): van der Stelt, C.; Haasjes, A.; Tersteege, H. M.; Nauta, W. Th.
CORPORATE SOURCE: N. V. Koninklijke Pharm. Fabrieken
SOURCE: Recueil des Travaux Chimiques des Pays-Bas (1965), 84(11), 1466-77
CODEN: RTCPA3; ISSN: 0165-0513
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB cf. CA 56, 7241d. The synthesis of several acids of the 5H-dibenzo[a,d]cycloheptene (I) series is described. 5H-Dibenzo[a,d]cycloheptene-5-acetic acid chloride (II) treated with SnCl4 yielded III which was converted by the reductive amination with MeNH2, Me2NH, and PhCH2CHMeNH2 to the corresponding IV. Several esters of aliphatic and heterocyclic amino-alcs. were prepared from the I acids. The acids were also converted to 4-substituted piperazides which were reduced to the corresponding piperazine derivs. 5-Chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (V) (55 g.) and 23 g. CuCN rapidly heated with stirring to about 90° (spontaneous temperature rise to about 150°), cooled with stirring to about 80°, and diluted with 125 cc. C6H6 yielded 40 g. 5-CN analog (VI) of V, m. 86-7° (ligroine). VI (67.5 g.), 135 cc. H2O, 135 cc. H2SO4 (d. 1.84) and 200 cc. AcOH refluxed 24 hrs. yielded 85% 5-CO2H analog (VII) of V, m. 220-2° (EtOH). 5-OH analog (VIII) (21 g.) of V in 105 cc. MeOH and 6 drops concentrated HCl refluxed 3 hrs. gave 21.5 g. 5-OMe analog (IX) of V, b0.001 138-40°. IX (21.5 g.) in 500 cc. Et2O and the alloy from 9.6 g. K and 2.4 g. Na refluxed 20 hrs. with stirring under N, treated with solid

CO_2, and diluted with 60 cc. EtOH and 200 cc. H_2O yielded 9 g. VII, m. 220-2° and 6.5 g. 10,11-dihydro-5H-dibenzo[a,d]cycloheptene (X), m. 73-5° (EtOH). 5-CH_2CHO derivative (88 g.) of X in 900 cc. EtOH and 110.5 g. $AgNO_3$ in 110 cc. H_2O treated dropwise with stirring below 30° with 90 g. KOH in 220 cc. H_2O and 870 cc. EtOH yielded 56 g. 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylideneacetic acid (XI), m. 167-70° (EtOH). XI (50 g.), 8 g. NaOH, and 250 cc. EtOH hydrogenated at 3 atmospheric over Raney Ni yielded 80% 5-CH_2CO_2H derivative (XII) of X, m. 159-61° (AcOEt). VIII (73.5 g.), 42.5 g. $NCCH_2CO_2H$, and 17 g. $ZnCl_2$ in 90 cc. AcOH refluxed 8 hrs. with stirring, poured into H_2O, and extracted with Et_2O, and the product refluxed 18 hrs. with 35 g. KOH, 17 cc. H_2O, and 70 cc. EtOH yielded 34 g. XII, m. 154-7° (AcOEt). Mg (6 g.), 40 g. $CH_2(CO_2Et)_2$; and 50 cc. absolute EtOH refluxed (the reaction was initiated by a few drops of CCl_4) until the Mg had dissolved and evaporated, the residue evaporated with 25 cc. dioxane, treated with 100 cc. dry tetrahydrofuran and 57.1 g. V in 200 cc. tetrahydrofuran, refluxed 4 hrs., and worked up, and the crude diethyl 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-malonate refluxed 10 hrs. with 50 g. KOH in 25 cc. H_2O and 100 cc. EtOH yielded 11 g. 5-EtO derivative; the acidified aqueous layer gave 59 g. 5-ethoxy-10,11-dihydro-5H-dibenzo [a,d]cycloheptenemalonic acid (XIII), m. 186° (decomposition) (AcOEt). XIII (55 g.) heated at 170° until the CO_2 evolution ceased gave 35 g. XII, m. 157-61°. V (6.9 g.) and 9.7 g. Cu derivative of $AcCH_2CO_2Et$ refluxed 6 hrs. with stirring in 80 cc. C_6H_6 gave 93% Et α-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)acetoacetate (XIV), m. 79-80° (petr. ether). XIV (9.7 g.) in 150 cc. EtOH and 150 g. 50% aqueous NaOH refluxed 3 hrs. yielded 4.2 g. oily 5-acetonylidene derivative of X, b3 155-60°, which with $NH_2OH.HCl$ in C_5H_5N gave the oxime, m. 99-102° (aqueous MeOH); the aqueous layer acidified yielded 54% XII. XIV (6.4 g.) in 100 cc. C_6H_6 refluxed 4 hrs. with 2.2 g. $PhNHNH_2$ gave 6.4 g. phenylhydrazone of XIV, m. 116-20° (EtOH). XII (15.2 g.), 10.7 g. $SOCl_2$, and 150 cc. C_6H_6 refluxed 2 hrs. and evaporated, the residue in 225 cc. refluxing C_6H_6 treated dropwise with 16.9 g. tropine in 40 cc. C_6H_6 and refluxed 3 hrs., and the oily product treated with $(CO_2H)_2$ in Et_2O gave 40% XV (R = 3α-tropanyl, X = C_2H_4, n = 1), (XVI), m. 221-2°. Similarly were prepared the XV listed in the table.

1-Methyl-piperazine (7 g.) in 50 cc. MePh containing 10 g. K_2CO_3 refluxed 3 hrs. with 16.0 g. V in 75 cc. MePh yielded 17.5 g. 1-(10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5-yl)-4-methylpiperazine (XIX), b2 198°, m. 107-9° (ligroine); hydrogen maleate, m. 145-7° (EtOH).

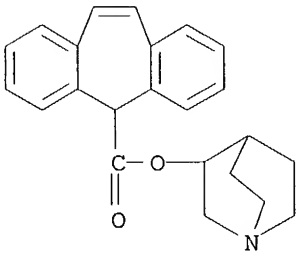
R, X, n, Salt with, M.p. of salt, % yield; $Me_2NCH_2CH_2$, CH_2CH_2, 0, HCl, 212-14°, 76; $Me_2NCHMeCH_2$, CH_2CH_2, 0, $(CO_2H)_2$, 211-13°, 84; $Et_2N(CH_2)_3$, CH_2CH_2, 0, HCl (XVII), 145-7°, 55; 1-methyl-3-pyrrolidyl, CH_2CH_2, 0, maleic acid, 143-5°, 63; 1-methyl-4-piperidyl, CH_2CH_2, 0, maleic acid, 162-3°, 72; 3 α-tropanyl, CH_2CH_2, 0, HCl (XVIII), 272-5°, 75; , , , MeBr, 288-93°, 90; 3β-tropanyl, CH_2CH_2, 0, maleic acid, 175-7°, 79; 3-quinuclidinyl, CH_2CH_2, 0, free base, 102-4°, 50; iso-Am, CH_2CH_2, 0, free base, (b0.2 160°), 70; $Me_2NCH_2CH_2$, CH:CH, 0, HCl, 206-8°, 75; 3α-tropanyl, CH:CH, 0, HCl, 289-92°, 60; 3-quinuclid-inyl, CH:CH, 0, free base, 150-2°, 60; 3-quinuclidinyl, CH_2CH_2, 1, HCl, 222-5°, 65; $Me_2NCH_2CH_2$, CH:CH, 1, HCl, 170-1.5°, 88; $Et_2N(CH_2)_3$, CH:CH, 1, $(CO_2H)_2$, 147-8°, 80; 1-methyl-4-piperidyl, CH:CH, 1, HCl, 192.5-4.5°, 70; 3α-tropanyl, CH:CH, 1, HCl, 237-9°, 20; Phenylpiperazine (6.5 g.) and 4.5 g. V heated 0.5 hr. at about 140° yielded 55% 4-Ph analog of XIX, m. 178-82° (C_6H_6-MeOH). Similarly was prepared the 4-$PhCH_2$ analog of XIX, 55%, m. 120-1°. VII (23.8 g.), 17.8 g. $SOCl_2$, and 120 cc. C_6H_6 refluxed 3 hrs. and evaporated, the residue dissolved in 75 cc. C_6H_6 and added dropwise to 10 g. 1-methylpiperazine, 75 cc. C_6H_6

and 28 cc. C5H5N, the mixture diluted after 1 hr. with H2O, and the crude product treated in dry Et2O with alc. HCl yielded 55% XX.HCl (X = CH2CH2, Y = CO) (XXI.HCl), m. 278-80° (EtOH). Similarly were prepared XX (X = CH2CH2, Y = CH2CO), 50%, isolated as the maleate, m. 173-4°, and XX (X = CH:CH, Y = CO), 55%, isolated as the maleate, m. 194-6°. The mother liquor from XXII yielded XXIII, m. 152-3°, b. 100-40°. XXI (10.7 g.) in 250 cc. Et2O added dropwise to 1.1 g. LiAlH4 in 100 cc. Et2O and refluxed 3 hrs., and the product treated with HCl-Et2O gave 55% XX.2HCl (X = CH2CH2, Y = CH2), m. about 265°. Similarly were prepared the XX listed in the 2nd table. II from 13.2g. XII in 100cc. CS2 added at -5° to 9g. AlCl3 in 200 cc. CS2 and stirred a-5° and then 2 hrs.at room temperature yielded 6.9 g. III, m. 213-15° (CHCl3-petr. ether) II in PhNO2 treated at room temperature with SnCl4 yielded 67% III. III (4.7 g.) and 6.2 g. X, Y, Salt, M.p. of salt, % yield; CH2CH2, CH2CH2, dihydrochloride, 280°, 55; CH:CH, CH2, dimaleate, 189-91°, 60; CH:CH, CH2CO, free base, 123-4°, 33; CH:CH, CH2CH2, free base, 59-60°, 85; , , dihydrochloride, 257-62°, , ; MeNH2 in 250 cc. BuOH hydrogenated 5 hrs. at 100°/50 atmospheric over 2 g. Raney Ni, and the crude product treated with HCl-Et2O gave IV (R = H, R' = Me). Similarly was prepared IV (R= R' = Me), 26%, isolated as the maleate, m. 180-2°. III (11.4 g.) and 6.6 g. PhCH2CHMeNH2 in 125 cc. dry xylene refluxed with the azeotropic removal of H2O, the crude product treated in 250 cc. EtOH below 30° with 2.5 g. NaBH4, kept 0.5 hr. at room temperature, refluxed 0.5 hr., and evaporated, and the residue shaken in Et2O with dilute HCl gave 40% IV (R = H, R' = PhCH2CHMe), m. 281° (decomposition).

IT **5093-06-1**, 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 3-quinuclidinyl ester **87395-65-1**, 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-, 3-quinuclidinyl ester
(preparation of)

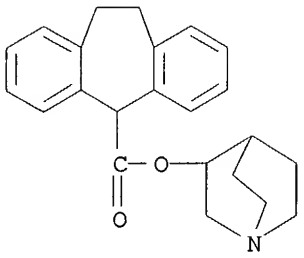
RN 5093-06-1 CAPLUS

CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 3-quinuclidinyl ester (7CI, 8CI) (CA INDEX NAME)



RN 87395-65-1 CAPLUS

CN 5H-Dibenzo[a,d]cycloheptene-5-carboxylic acid, 10,11-dihydro-, 1-azabicyclo[2.2.2]oct-3-yl ester (9CI) (CA INDEX NAME)



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L3 107 S L1 FULL

FILE 'CAPLUS' ENTERED AT 11:53:59 ON 12 JUL 2004
L4 27 S L3

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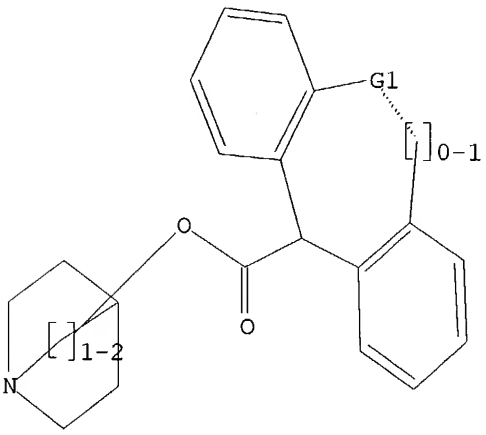
L1 STR



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60525215	Not Issued	020	11/26/2003	(WHOLE) ASSEMBLE VIVEVERSA ONE-PIECE HOE-RAKE-ACUTE PICKET TOOL	FERN MARI PAZ
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